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Additive manufacturing in pharmaceutical formulation - Development of biodegradable printed dosage forms for oral drug delivery

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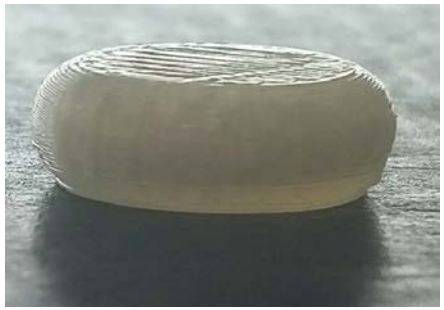
ADDITIVE MANUFACTURING IN PHARMACEUTICAL FORMULATION -
DEVELOPMENT OF BIODEGRADABLE PRINTED DOSAGE FORMS FOR ORAL DRUG DELIVERY



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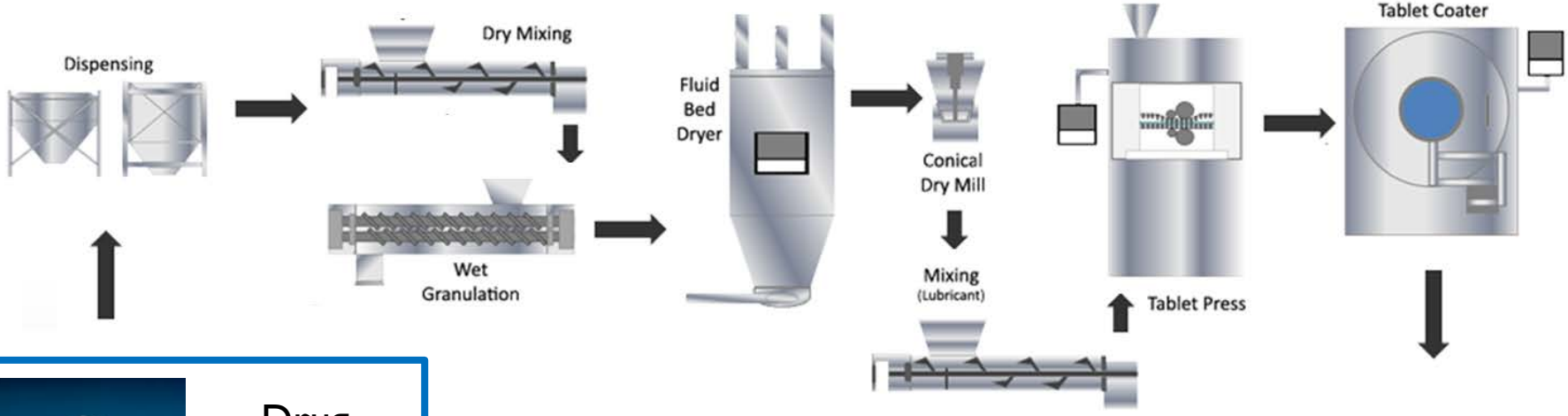
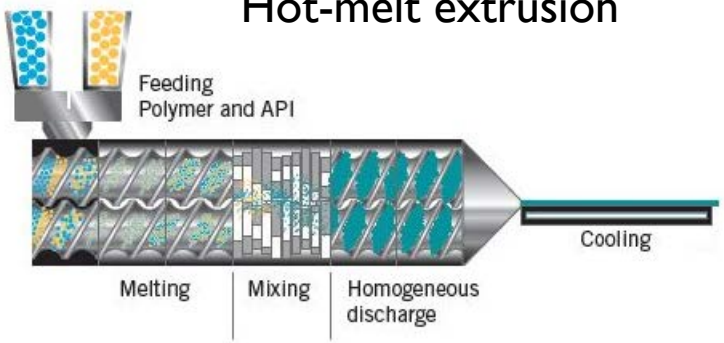
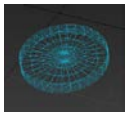
Process outline - comparison



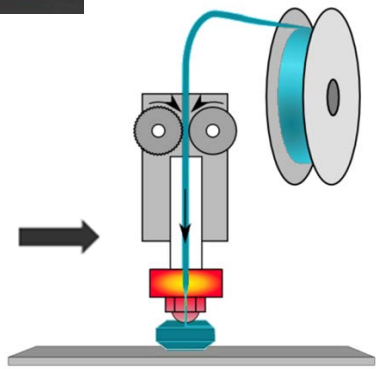
Drug
+
Excipients

Hot-melt extrusion





3D printing (FDM)

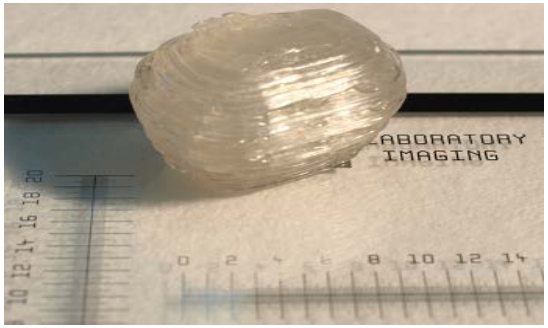


Tablets

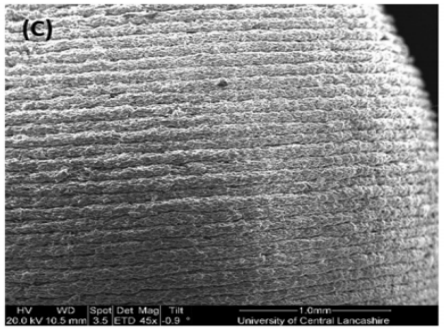
Motivation + advantages

- Personalized dosing, flexibility
- Multi-drug loading, multilayer tablets (multiple nozzles)
- Adjustable geometry and porosity (=> dissolution rate)
- Potential for scale-up (printhead arrays)
- August 2015 – First commercial application - Spritam (Levetiracetam) approved by FDA

FDA-approved Spritam tablets



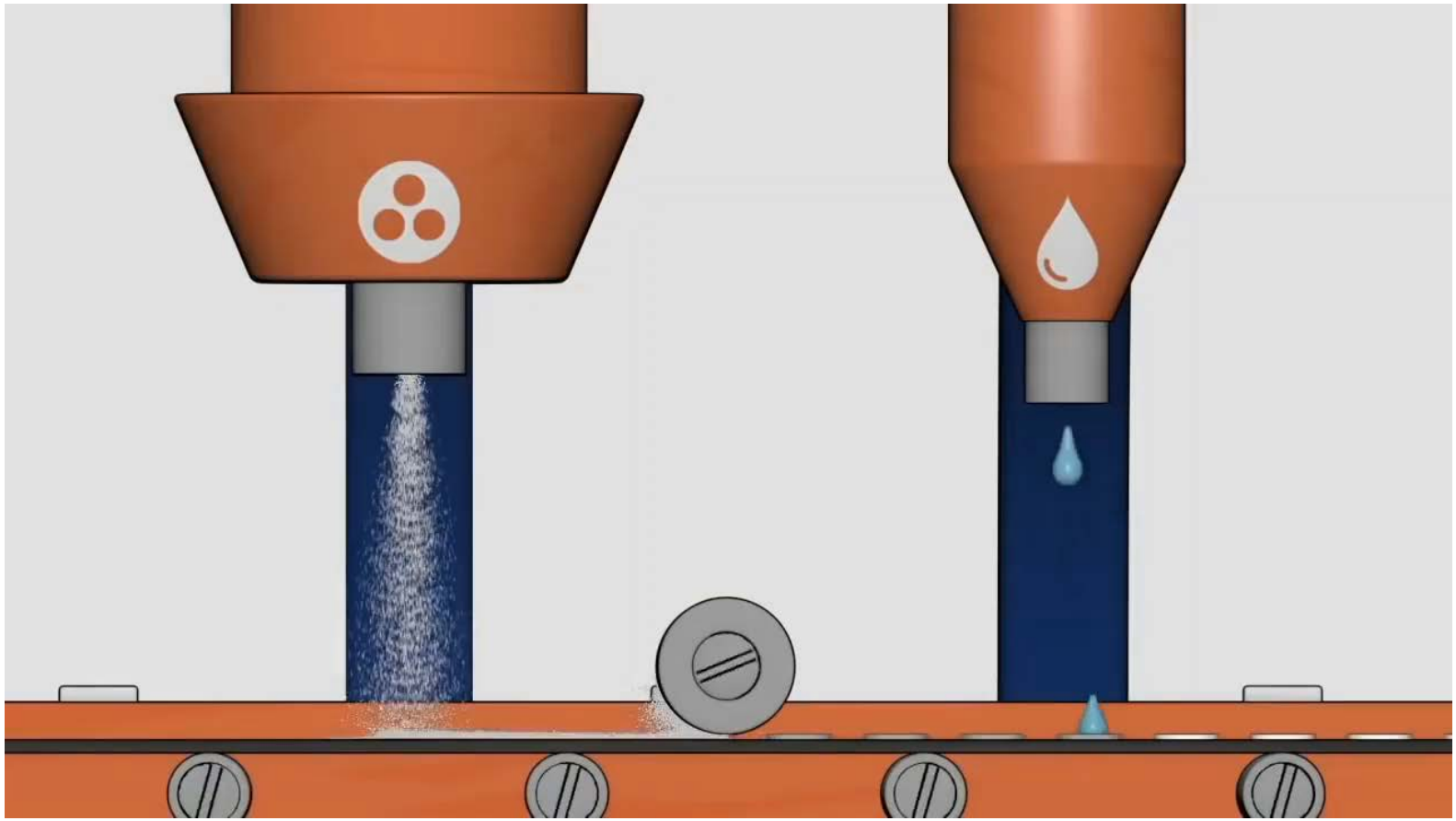
FDM-printed tablet



Surface of a FDM tablet (SEM)

ZipDose Technology

- First approved 3D-printed dosage form
- High dose of the drug Levetiracetam, immediate release

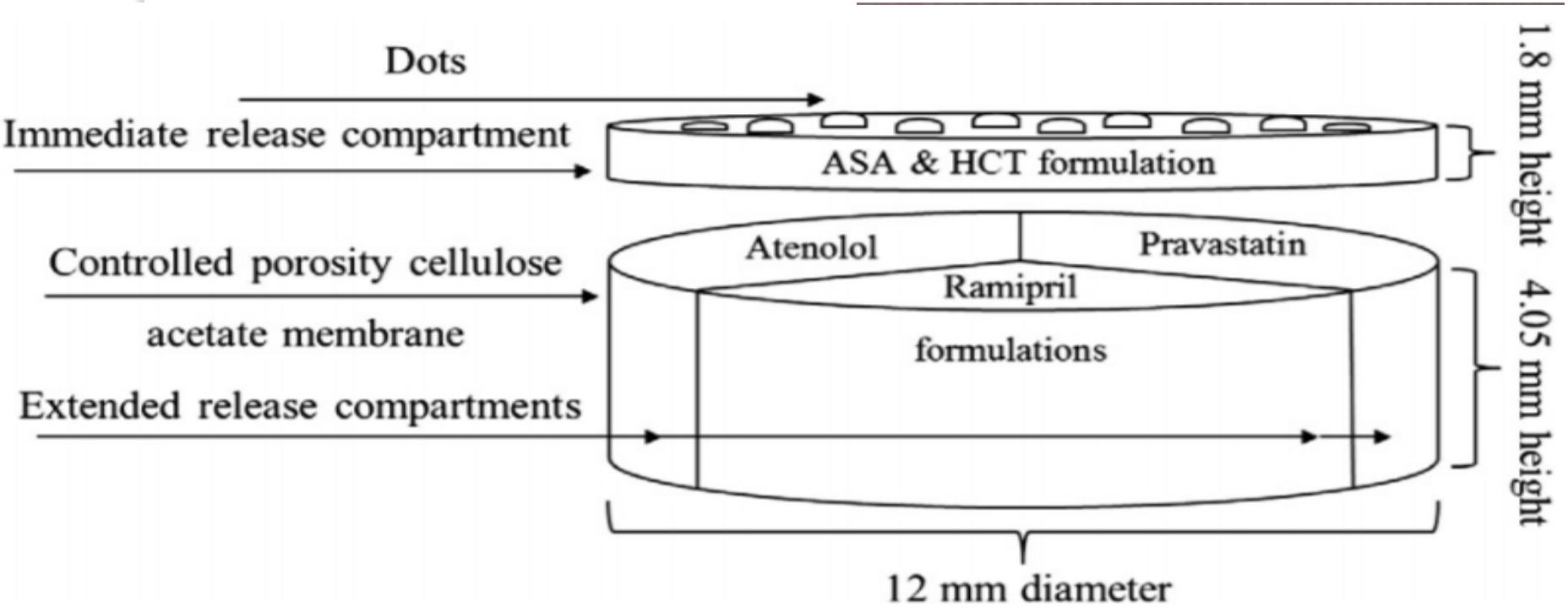


ZipDose Technology

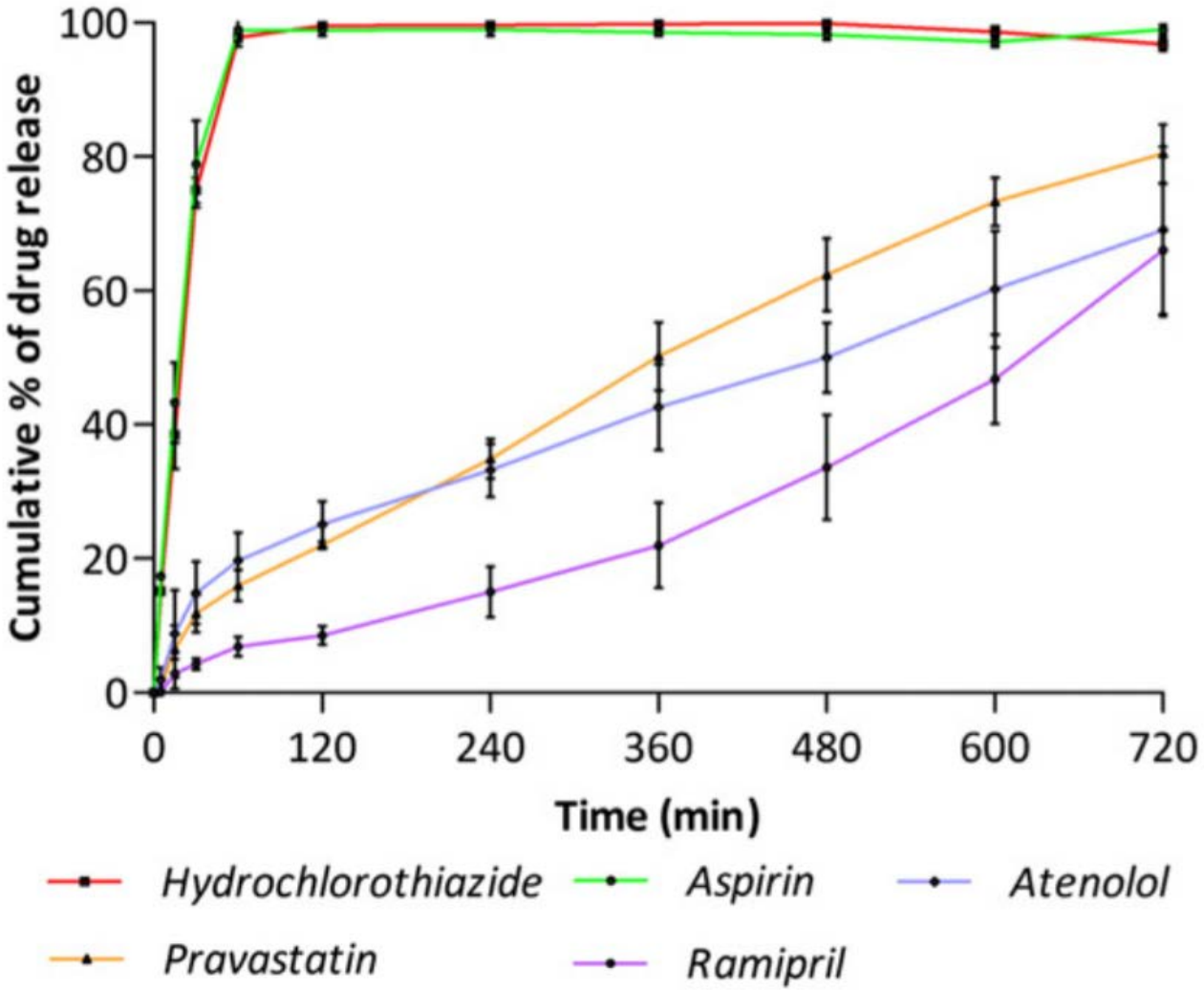
- First approved 3D-printed dosage form
- High dose of the drug Levetiracetam, immediate release

Solid paste extrusion

- Easy formulation (drug can be in a dispersion)
- No thermal processing, but time-consuming paste preparation
- Multitablet – up to 5 different drugs with varying release rates

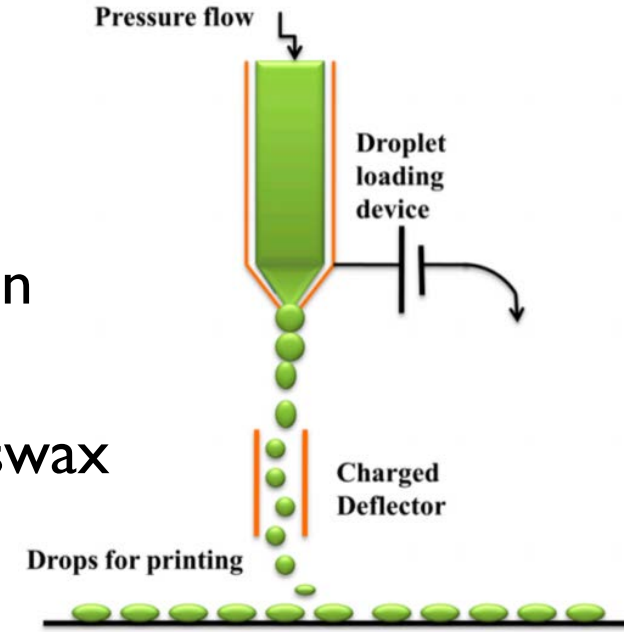


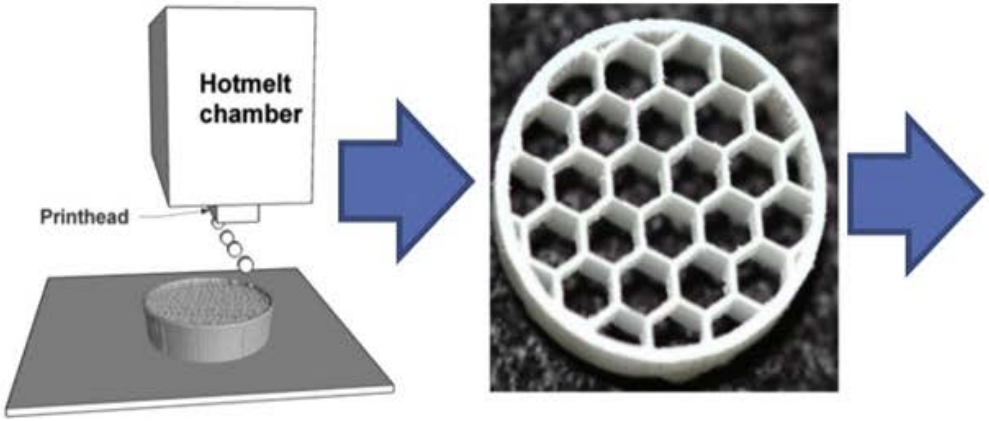
Solid paste extrusion

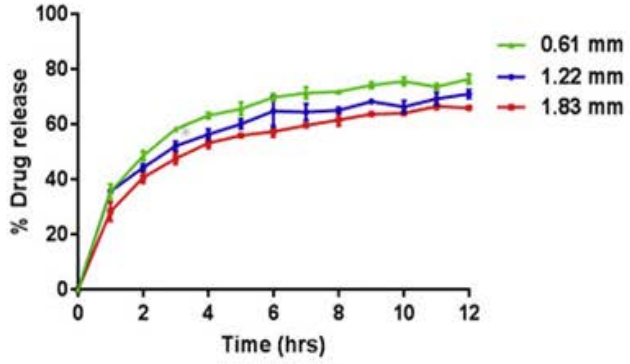


Ink-jet 3D printing

- High resolution (30µm)
- Time-consuming process, friability
- Typically involves solvent evaporation
- Example:
  Heated chamber, Fenofibrate + beeswax

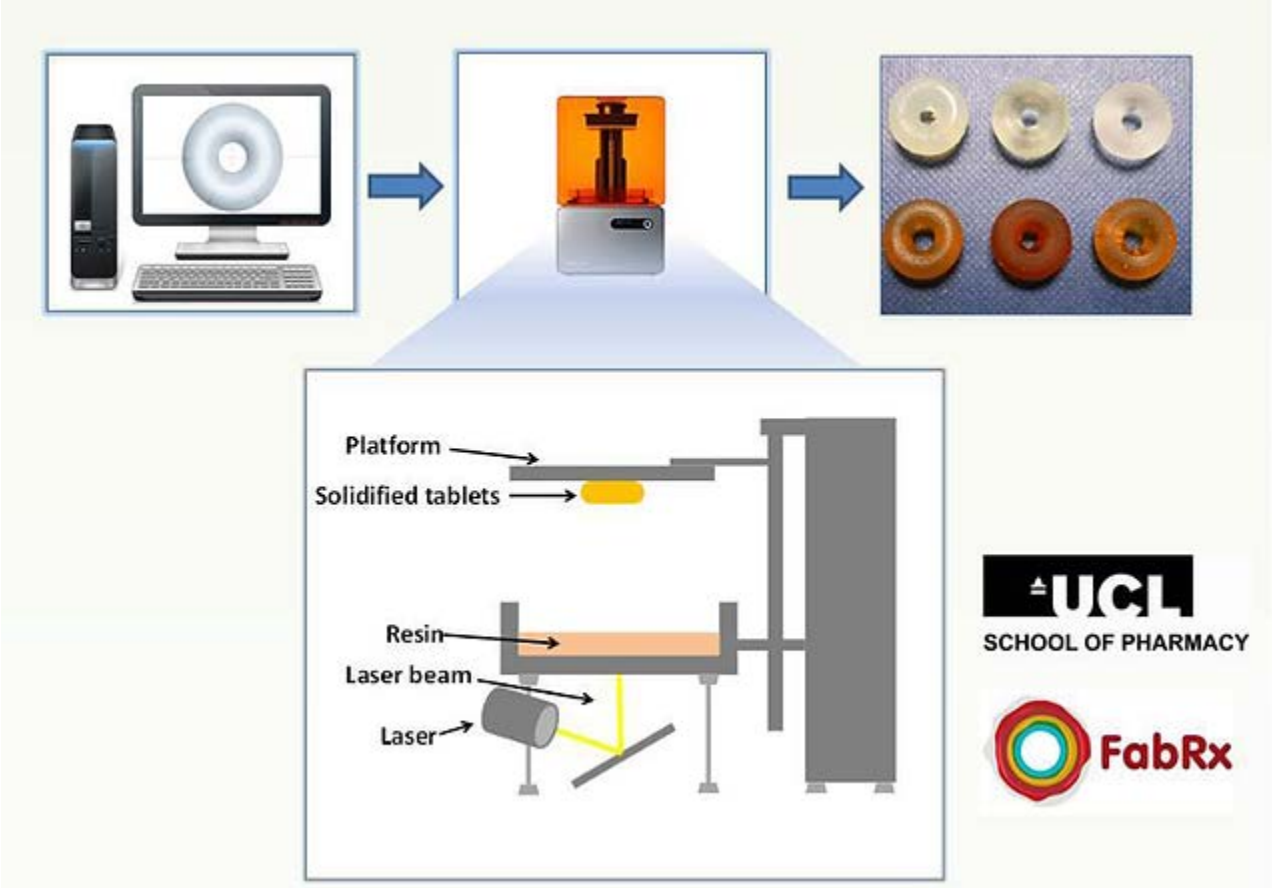






Stereolitography (SLA)

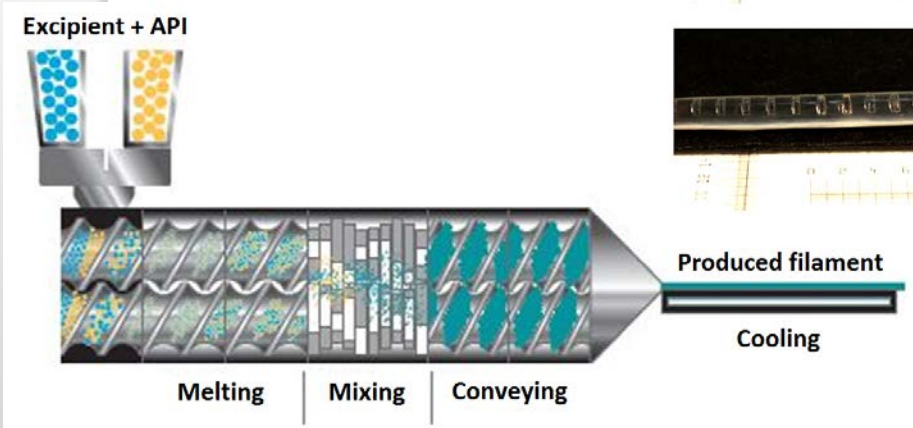
- Excipients – photo-curable resins => UV radiation
- High resolution (10µm), no external heating
- "Applicable" for most drugs, UV-drug interaction poses risk

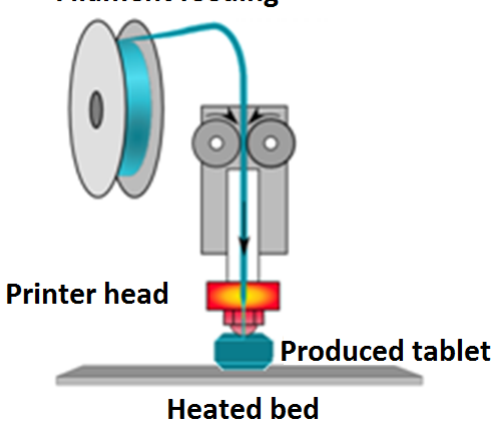


Selective light sintering (SLS)

- Sintering of excipients + drug in powder form
- Material loss, rinsing step
- Example: Kollicoat IR, Eudragit L100-55 + Paracetamol

Fused deposition modelling





General filament composition

- An approved drug (API)

  - thermal stability of the molecule

- Polymer matrix (Soluplus, Eudragit XX, Kollidon XX, cellulose derivates)

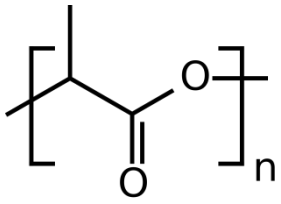
  - biodegradable approved excipients, solubilize/amorphize the drug

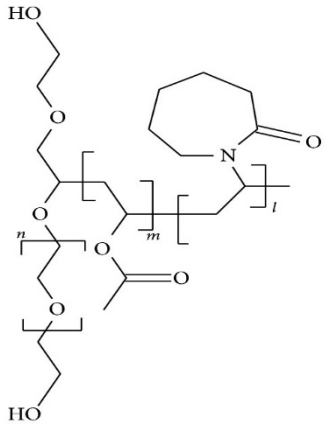
  - suitable thermal and rheological properties

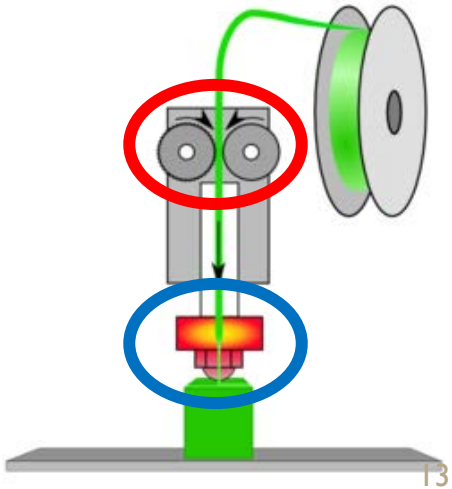
- Functional additives – plasticizers (PEG XX, glycerol, …), glidants/anticaking agents (Talcum, MgStearate), disintegrants (Ac-Di-Sol, starch), desiccants (citric acid anhydrous)
  - affect mechanical properties of the filaments, process temperature, properties of the powder form, dissolution / disintegration kinetics

Important filament properties & extrusion parameters

- Mechanical properties (Young‘s modulus, hardness)
- Shape homogeneity (affected by extrusion parameters)
- Heat transfer rate (heating & cooling)
- Surface roughness / stickiness
- Lowest achievable process temperature
- Homogeneity of composition (drug content)
- Drug structure (amorphous / crystalline) and stability
- Dissolution / disintegration rate







Pharma-grade hot-melt extrusion

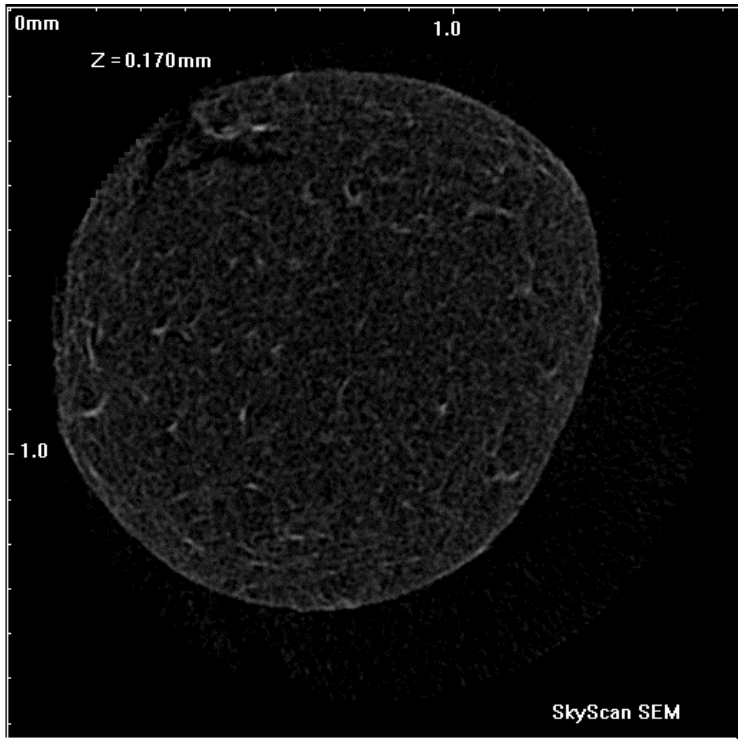
=> Anticaking agents (glidants)

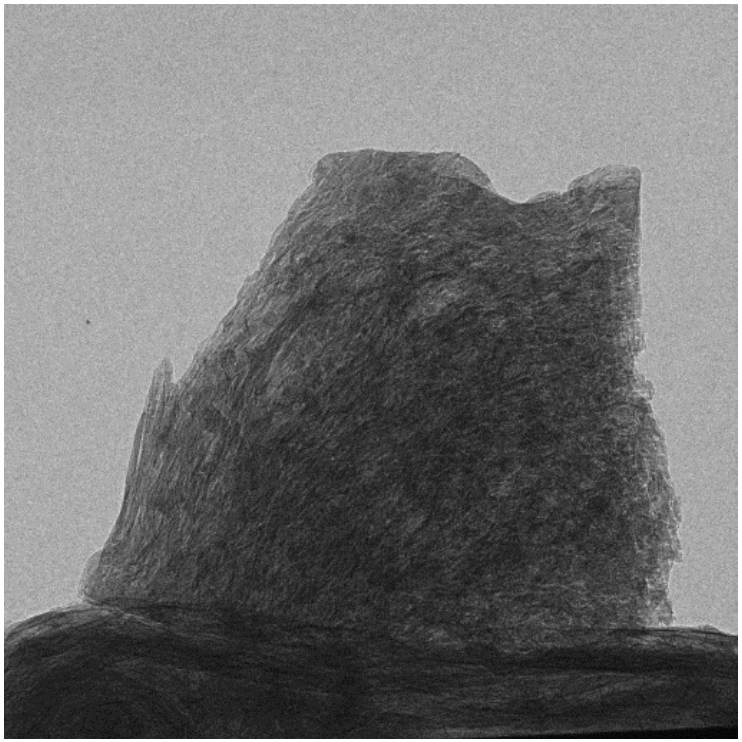
- Filament cooling
- Filament conveying
- Powder agglomeration
- Cavity formation

Rheology of the powder form

Inner structure of the filaments

- Mechanical properties affected by microporosity (in some cases up to 40% v/v)
- Micro-CT, Image analysis and reconstruction
- Porosity lowered by adding dessiccants or glidants

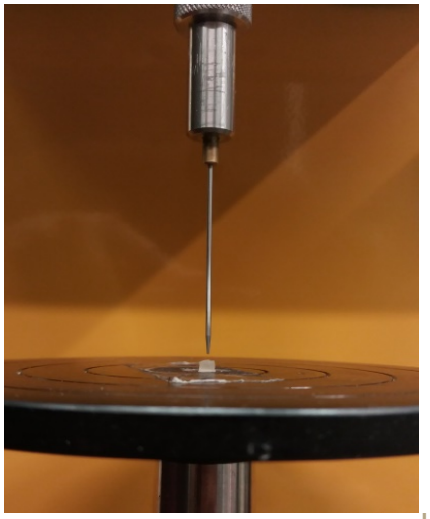




Important filament properties & extrusion parameters

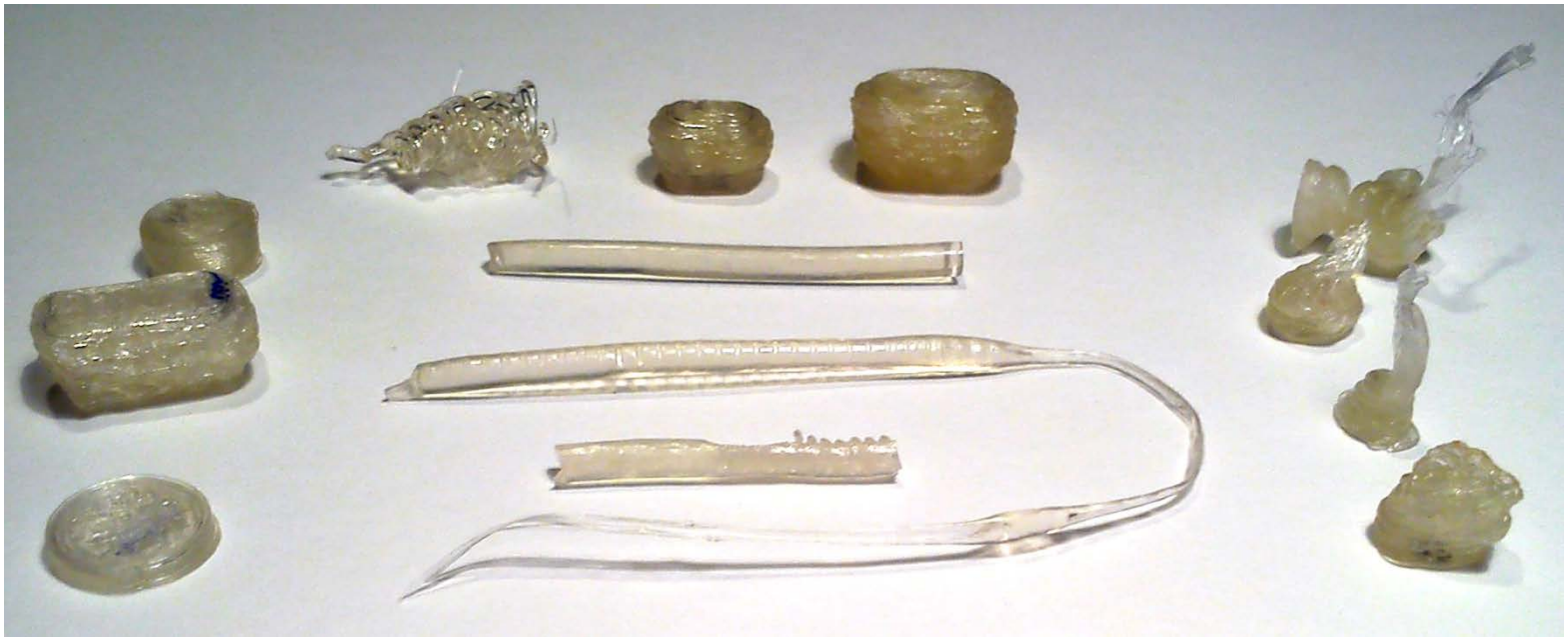
Property	Value and units	Method
Elasticity modulus	55.65 ± 3.31 kN/m	Three-point bending test
Indentation hardness	62.58 ± 5.07 kN/m	Needle-probe test
Normalized viscosity at 145 °C	10658 ± 1308 Pa·s	Rotational rheometry
Thickness uniformity	2911 ± 31 μm	Digital caliper
API content uniformity	9.96 ± 0.53 % wt.	HPLC + UV spectroscopy

Component	Mass fraction (%)
Valsartan	10 - 40
HPC EF	20 - 80
Soluplus	0 - 55
Peg 6000	1 - 8
Citric acid	0 - 3
Magnesium St.	0 - 8

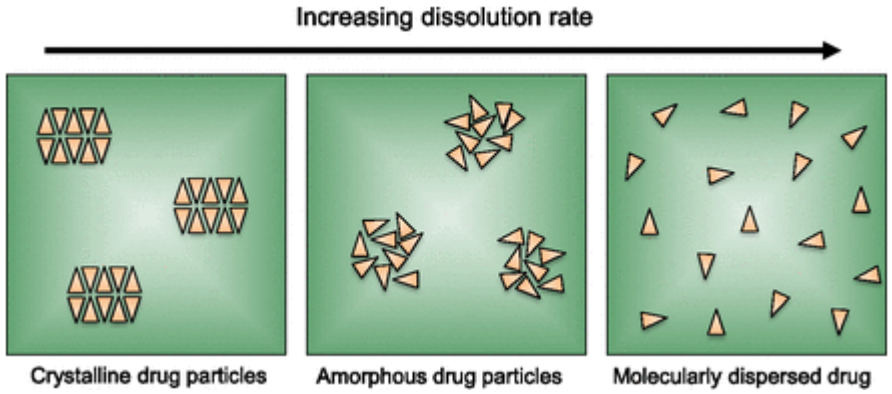


Printing parameter adjustment

- Gear speed, inner filling characteristics, nozzle movement speed, filament retraction, perimeter characteristics, …
- Printing temperature, bed temperature, …
- Printing resolution distribution, layer overlap, nozzle distance, …

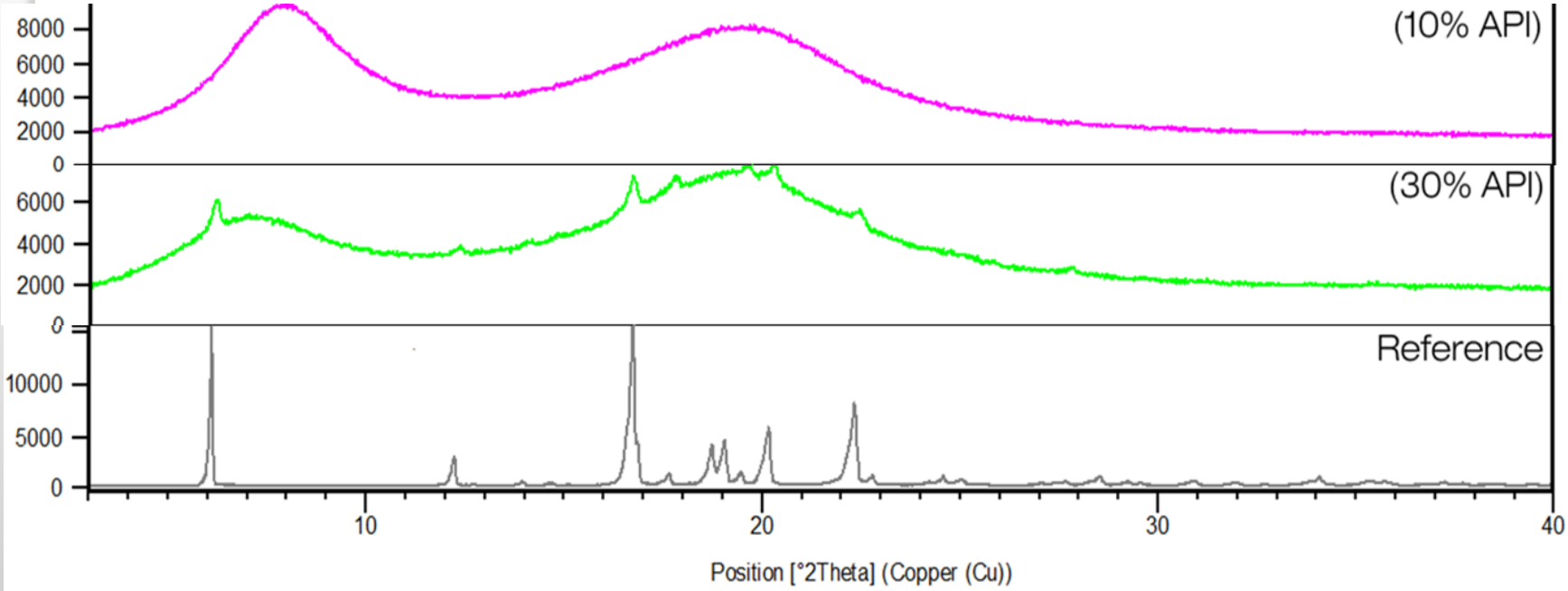


Drug structure analysis



- Amorphous / crystalline after extrusion?

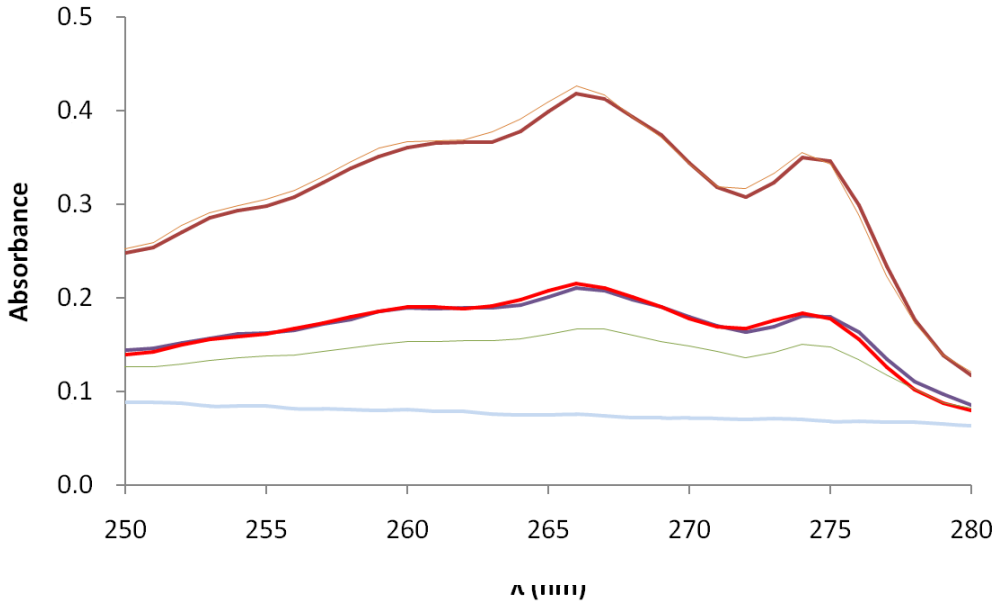
=> X-ray powder diffractometry, differential scanning calorimetry



Homogeneity of drug content

UV spectroscopy:

- Absorpce of excipients
- Light scattering
- Solubility

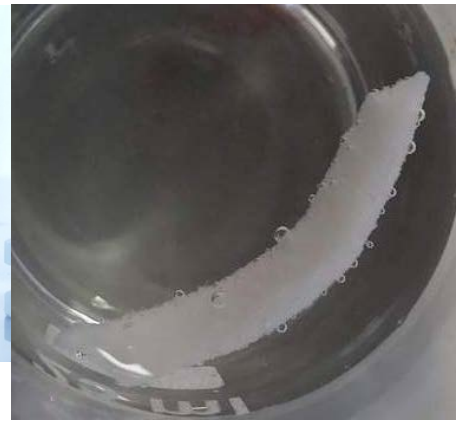


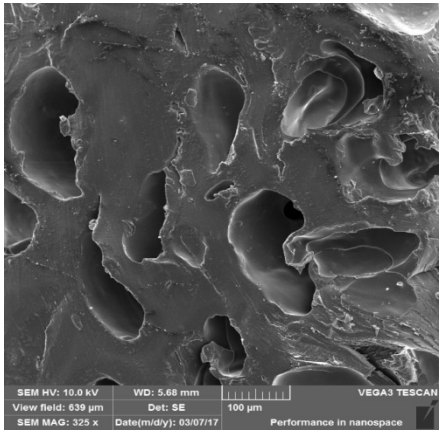
HPLC:

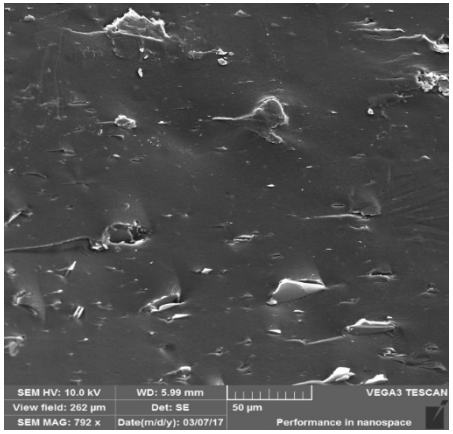
Initial content (%)	Measured content (%)
30	29.7 ± 0.9
10	9.5 ± 2.6
10	10.3 ± 0.2
15	14.4 ± 4.0

Disintegration enhancement

=> Effervescent compounds – disintegration due to CO_2 production, but leads to increased porosity and brittleness





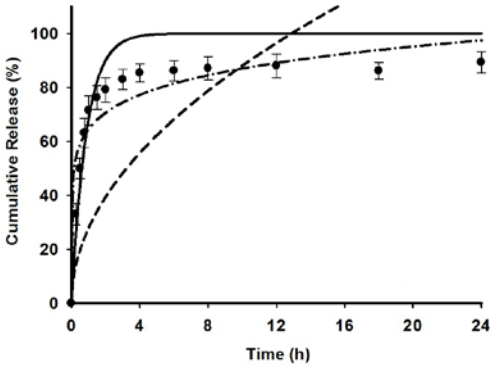


„Exploding“ effervescent tablet

- Hollow tablet filled with effervescent mixture

Virtual prototyping and parametric design of 3D printed tablets based on the solution of inverse problem

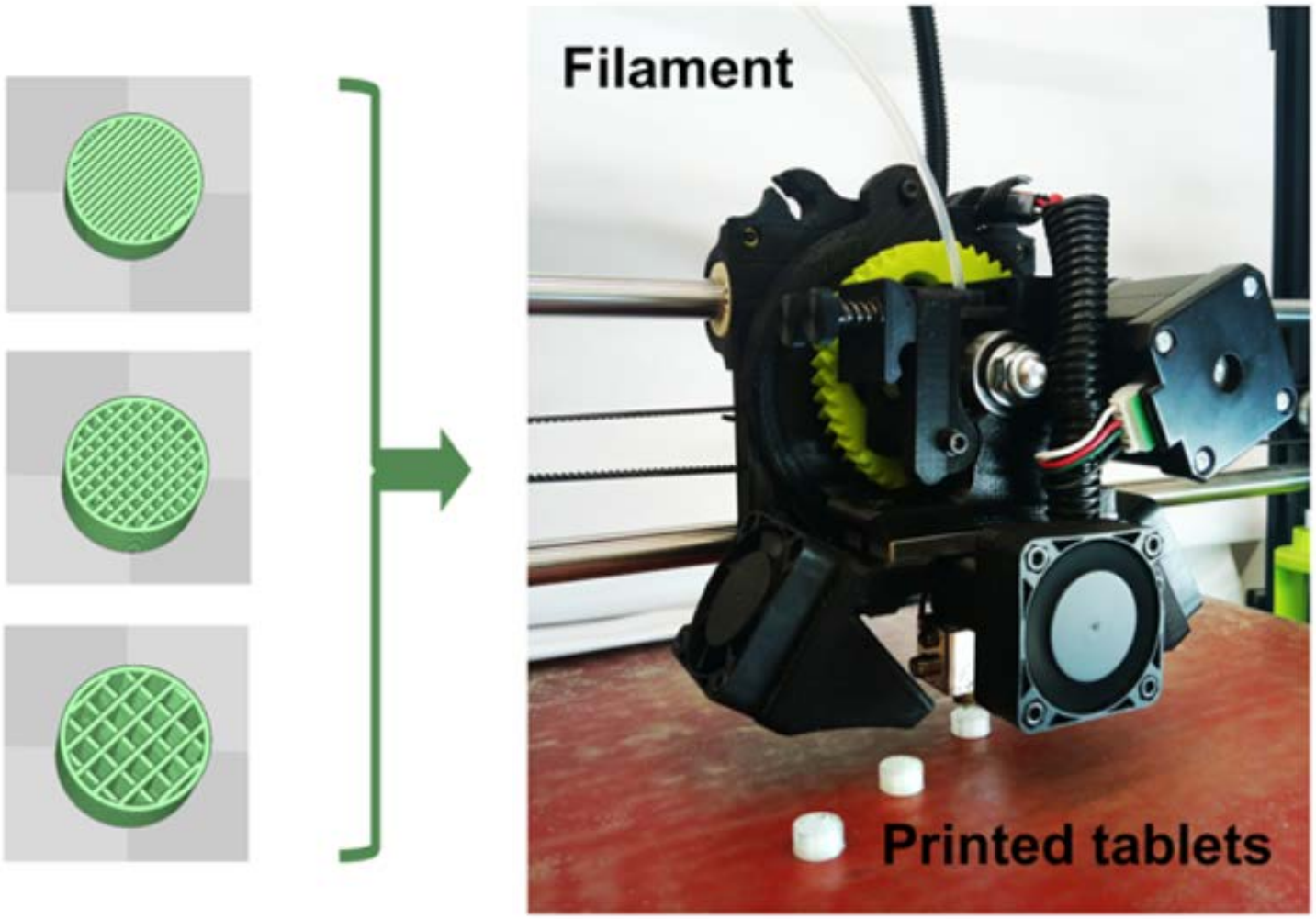
Desired result



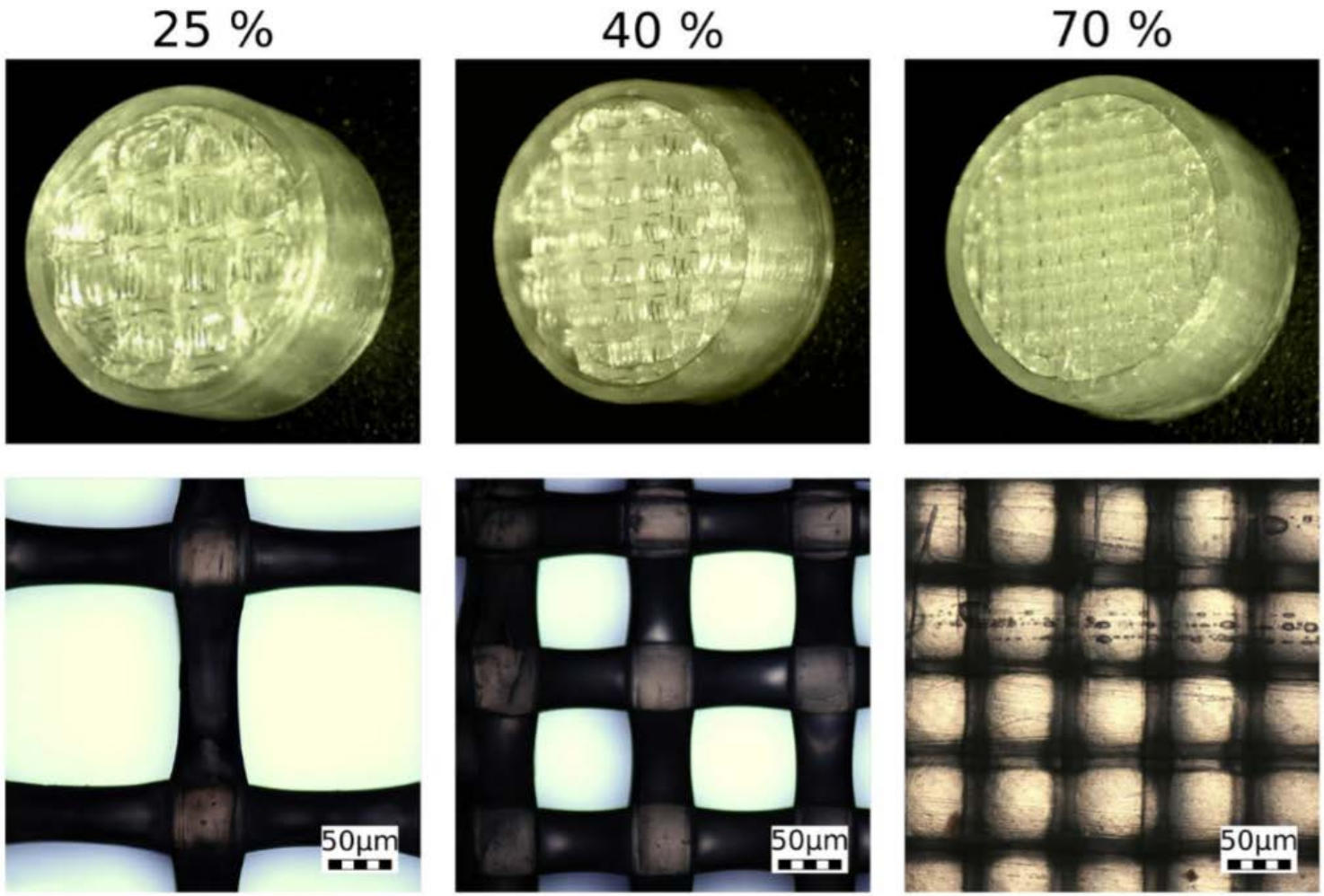
Initial product parameters

1) Parametric series of tablets with varying internal porosities
   => library of dissolution profiles, superpositions
2) Adjusting parameters of a mathematical model to accurately predict dissolution and intrapolate between measured data
3) Superpositions of different porosities to achieve new release profiles
4) A desired release profile met by iterative programming
   => tablet design and printing, experimental verification

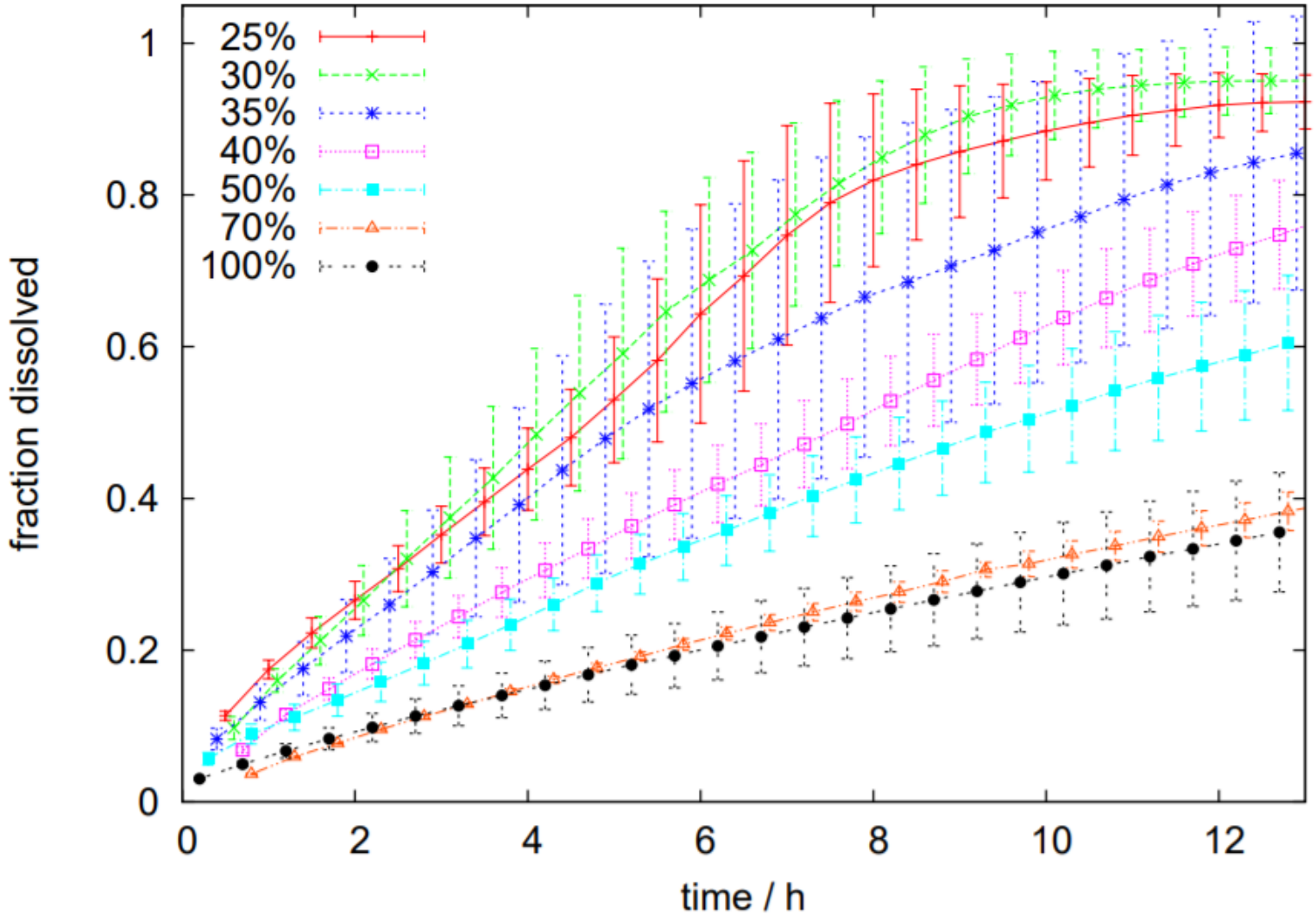
Virtual prototyping and parametric design of 3D printed tablets based on the solution of inverse problem



Virtual prototyping and parametric design of 3D printed tablets based on the solution of inverse problem



Dissolution of single-porosity tablets



Model overview, parameter fitting

Dimension form **Dimensionless form**

Diffusion flux between voxels:

$$N_{ij} = D\frac{c_i - c_j}{h}h^2 \qquad \hat{N}_{ij} = \left(\frac{D\tau_0}{h^2}\right)(\hat{c}_i - \hat{c}_j)$$

$$\hat{c} = c/c^\star$$

API component balance in pore voxels:

$$h^3\frac{\mathrm{d}c_i}{\mathrm{d}t} = \sum_j N_{ij} \qquad \frac{\mathrm{d}\hat{c}_i}{\mathrm{d}\hat{t}} = \sum_j \hat{N}_{ij}$$

$$\hat{t} = t/\tau_0$$

API component balance in tablet voxels:

$$\frac{\mathrm{d}n_i}{\mathrm{d}t} = \sum_j N_{ij} \qquad \frac{\mathrm{d}\hat{n}_i}{\mathrm{d}\hat{t}} = \sum_j \hat{N}_{ij}$$

$$\hat{n} = n/(h^3 c^\star)$$

Boundary conditions:

at pore/tablet interface

$$c_i = c^\star \qquad \hat{c}_i = 1$$

at pore/external boundary interface

$$c_i = 0 \qquad \hat{c}_i = 0$$

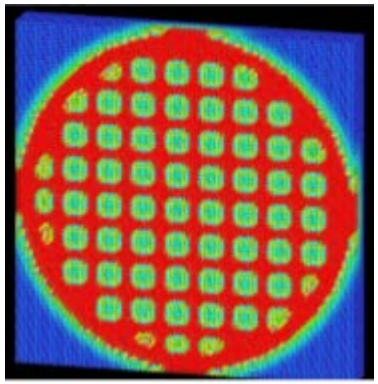
Initial conditions:

in pore voxels

$$c_i(0) = 0 \qquad \hat{c}_i(0) = 0$$

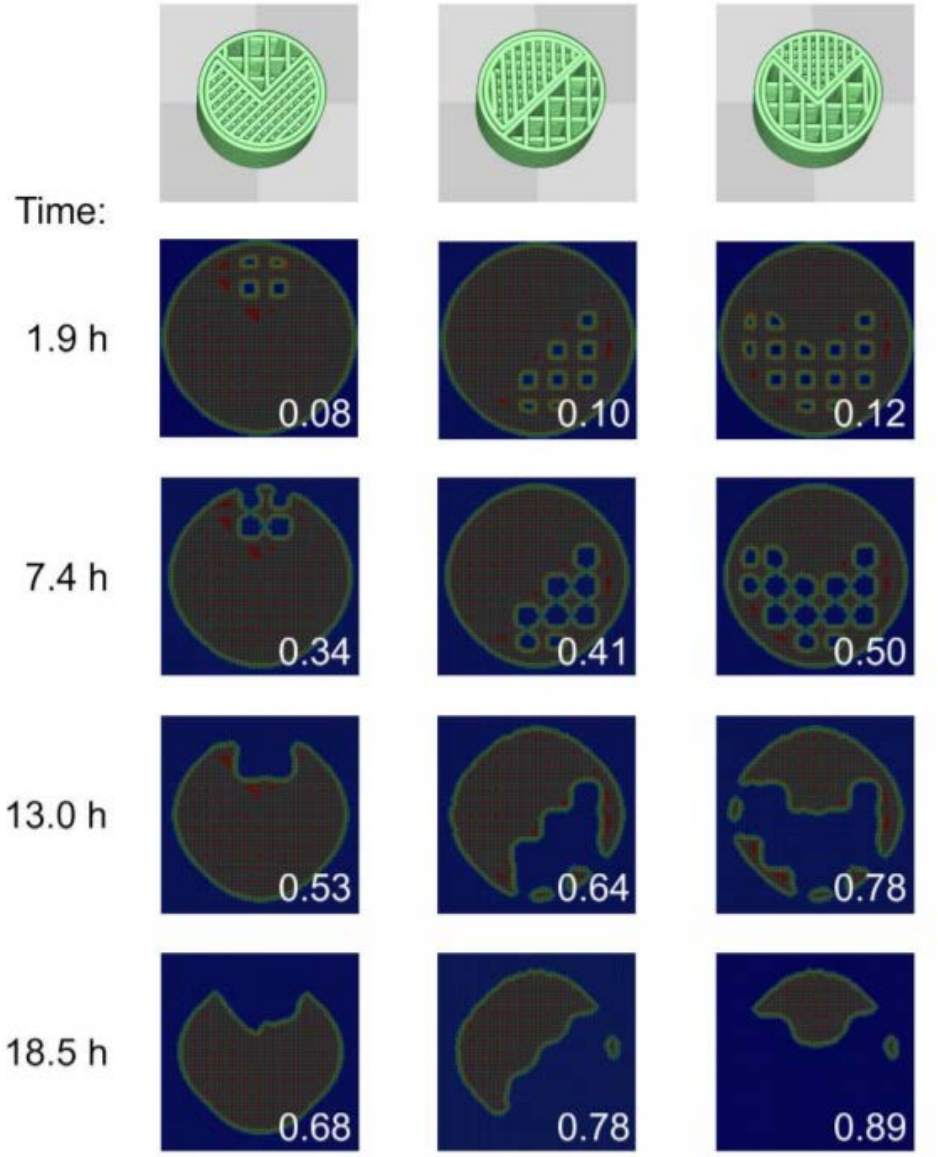
in tablet voxels

$$n_i(0) = \alpha c^\star h^3 \qquad \hat{n}_i(0) = \alpha$$



$$\alpha = \frac{\rho}{M\,c^\star}$$

Model overview, parameter fitting



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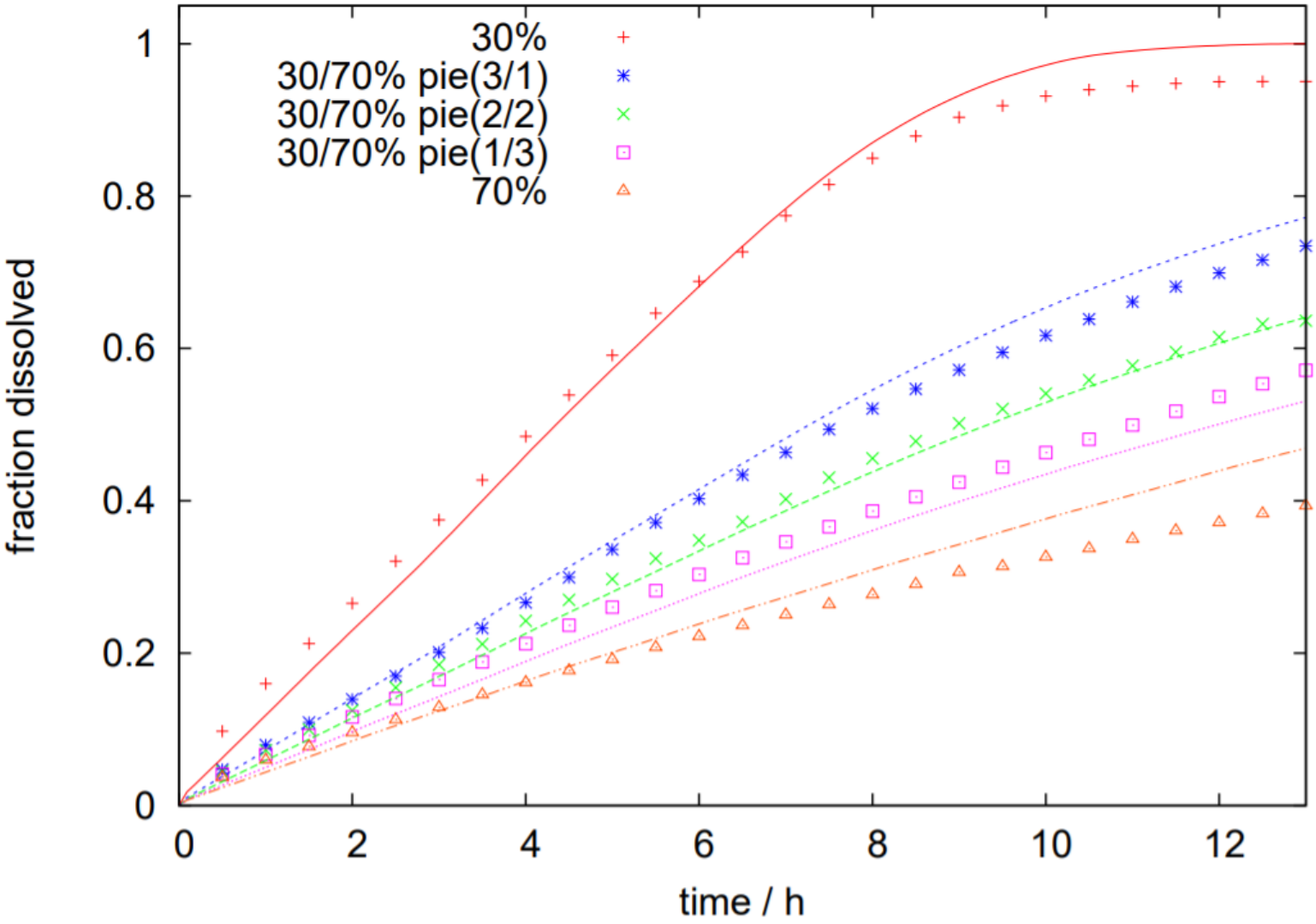
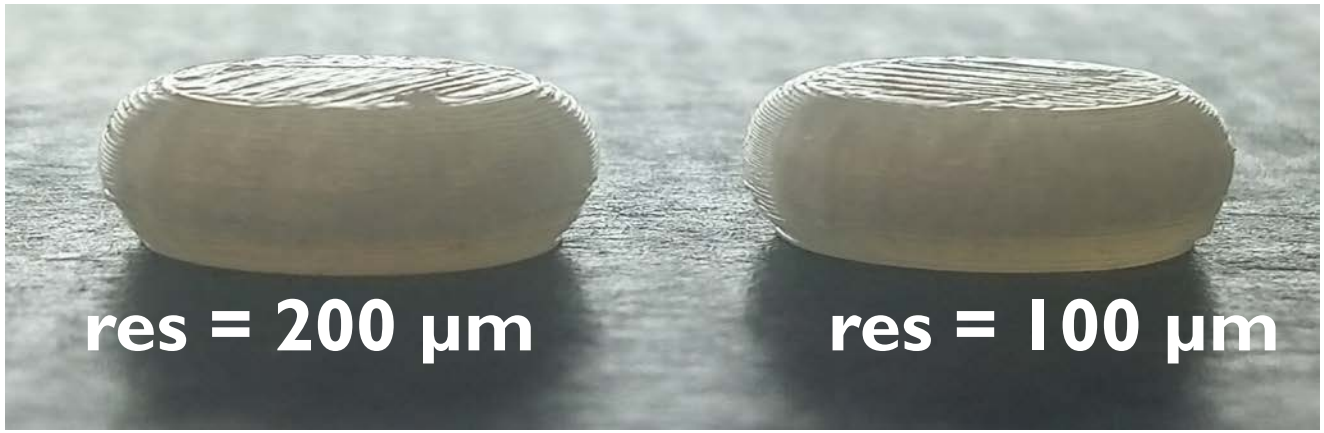


$(D = 1.8 \times 10^{-10}\ \mathrm{m}^2/\mathrm{s};\ \text{boundary layer} = 3)$

Conclusion

- Parametric study of composition and process parameters led to achieving FDM printability of 8 drugs
- Products analyzed (homogeneity, drug structure, material porosity, powder rheology, mechanical stability, in vitro dissolution, …)
- Dissolution kinetics predicted through mathematical 3D modelling, linked to tablet structure
- Employing genetic (evolutional) algorithm to find desired tablet structure
- Mapping and predicting "printability" for new drugs



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